**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| **In re Application of:** | Linda M. Pacioretty *et al.* |
| **Application No.:** | 10/699,195 |
| **Filing Date:** | 10/31/2003 |
| **Docket Number:** | CLANACCR_001NP |
| **Title:** | **COMPOSITIONS AND METHODS FOR THE TREATMENT OF HIV-ASSOCIATED FAT MALDISTRIBUTION AND HYPERLIPIDEMIA** |
| **Examiner:** | Chong, Young Soo |
| **Art Unit:** | 1617 |

**CERTIFICATE OF TRANSMISSION**

I hereby certify that this correspondence is being deposited with the United States Postal Service as "EXPRESS MAIL" MAILING LABEL NUMBER **EO 989 186 895 US** in an envelope addressed to MAIL STOP, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

Date: 2/14/11

John G. Babish

**MAIL STOP**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**DECLARATION PURSUANT TO 37 C.F.R. § 1.132**

I, John G. Babish declare as follows:

1. I am Dr. John G. Babish, Chairman, Bionexus, Ltd. I have held this position since June 1997.

2. I have Doctorate and Masters degrees, respectively, in Biochemistry and Chemistry from Cornell University, as well as a Bachelor degree in Biochemistry from The Pennsylvania State University.

3. On the basis of 30 years of training, 106 peer-reviewed research publications, grants and experience, I am an expert in the art of molecular biology of pharmaceuticals and xenobiotics. A copy of my Curriculum Vitae is attached as Exhibit A.

4. Additionally, I have served as Senior Pharmacologist in two clinical studies involving the testing of dietary supplements in HIV-positive subjects. In one of these studies, conducted during the filing of the instant application, the objective was to assess the effects of a supplement formulation on lipodystrophy (fat maldistribution) in HIV-positive subjects receiving highly active anti-retroviral treatment (HAART). During the two-year course of this study, I developed an understanding of the clinical presentation of lipodystrophy (fat maldistribution) and hyperlipidemia associated with anti-retroviral treatment of HIV infection and the response of these metabolic disturbances to dietary supplements.

5. I am co-inventor with Dr. Linda M. Pacioretty on the instant application and I am also a co-inventor on 32 domestic patents and 40 domestic patent applications.

6. I understand that in the course of the Office Action mailed November 15, 2010, the Examiner requested a DECLARATION UNDER 37 CFR 1.132 to compare the claimed subject matter with the closet prior art in order to be effective to rebut a prima facie case of obviousness. I also understand that it is the Applicant's burden to explain any proffered data and establish how any results should be taken to be ***unexpected*** and ***significant.*** Additionally, I will compare the claimed invention with prior art that is closer than that applied by the examiner.

7. In this Declaration, I will provide evidence of inoperability of the prior art and unexpected results of our own clinical trials thus demonstrating how the claims of the instant application continue to address a significant and unfulfilled need in the patient population.

***7.1. Inoperability of the prior art***

7.1.1. **Conjugated linoleic acids (CLA) cause lipodystrophy in mice.** A published mouse study described the loss of adipose tissue, hepatomegaly, the upregulation of TNFα, and development of lipodystrophic diabetes in mice administered CLA in the diet. Seven-week old, female C57/B6 mice were fed a standard laboratory diet supplemented

with 1% CLA for four days to eight months [Tsuboyama-Kasaoka, N., Takahashi, M., Tanemura, K., Kim, H. J., Tange, T., Okuyama, H., Kasai, M., Ikemoto, S., and Ezaki, O. Conjugated linoleic acid supplementation reduces adipose tissue by apoptosis and develops lipodystrophy in mice. *Diabetes* **2000**, *49*, 1534-42]. The study concludes, "This article reports the first observation that a dietary component causes lipodystrophy and suggests that some agents that decrease fat mass may lead to lipodystrophy."

7.1.2. **A meta-analysis reveals CLA fail to lower blood lipids in normal, human subjects, may be harmful to human health and may induce lipodystrophy and insulin resistance.** At the time of the claimed invention seven of eight published clinical studies (86%, a super majority) indicated a lack of effect of CLA on lowering blood lipids [reviewed in Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41]. The authors of this review concluded, "the evidence from human, short-term studies suggest that CLA supplementation **does not reduce body fat or increase fat-free mass.** There is evidence that CLA isomers sold as dietary supplements have marked biological effects, but there is accumulating evidence that the CLA t10,c12 isomer may adversely influence human health by **producing lipodystrophy** and insulin resistance."

7.1.3. **Further reviews of CLA research in patients with metabolic syndrome and diabetes confirm adverse, clinical effects of CLA in a variety of human conditions including diabetes.** A second, later and more inclusive meta-analysis of CLA effects in humans [Salas-Salvado, J., F. Marquez-Sandoval, et al. (2006). "Conjugated linoleic acid intake in humans: a systematic review focusing on its effect on body composition, glucose, and lipid metabolism." Crit Rev Food Sci Nutr **46**(6): 479-488], including healthy humans or patients with overweight, obesity, metabolic syndrome, or diabetes, concluded, "there is not enough evidence to show that conjugated linoleic acid has an effect on weight and body composition in humans. However, some of these studies have observed that the administration of various CLA isomers has adverse effects on lipid profile (it decreases HDL cholesterol concentration and increases Lp(a) circulating levels), glucose metabolism (glycemia, insulinemia or insulin sensitivity), lipid oxidation, inflammation, or endothelial

function. Of the 21 studies reviewed with information on lipid profiles, 15 indicated no effect (15/21), while six reported an adverse effect (6/21) of CLA. Thus, the preponderance of clinical evidence (86% in one study and 100%) supports the conclusion that CLA alone is not an effective treatment for hyperlipidemia.

7.1.4. **Inoperability of CLA.** At the time of the claimed invention, the use of CLA in the described patient population would not have been expected to resulted in a decrease in plasma lipids or gain in subcutaneous fat due to previously disclosed prior art describing (1) no clinical effect of CLA on blood lipids in normal subjects, (2) the potential for the CLA to induce lipodystrophy and insulin resistance in humans, and (3) additional prior art describing the loss of adipose tissue, hepatomegaly, and development of lipodystrophy in mice administered CLA. Considering the prior art, one of ordinary skill would deem CLA to be of significant potential harm to the patient population.

7.1.5. **N-acetylcysteine (NAC) and antioxidants decrease insulin sensitivity and have no effect on blood lipids in the patient population.** Prior art also teaches that a 24-week antioxidant supplementation, including NAC increased fasting glucose, insulin and HOMA (homeostasis model assessment) scores reflecting an increased insulin resistance and had no effect on LDL, HDL or triglycerides in HIV-infected subjects with lipoatrophy[McComsey, G., Southwell, H., Gripshover, B., Salata, R., and Valdez, H. Effect of antioxidants on glucose metabolism and plasma lipids in HIV-infected subjects with lipoatrophy. *J Acquir Immune Defic Syndr* **2003**, *33*, 605-7].

7.1.6. **Conclusion on the inoperability of the prior art.** Taken together these references indicate that the use of CLA or NAC in the disclosed patient population would be expected, by one of ordinary skill in the art, to be potentially harmful; and any beneficial effect of CLA either alone or in a combination with NAC in the patient population would be unexpected and provide a significant, unfulfilled need in the patient population.

**7.2. *Evidence of unexpected clinical results***

7.2.1. At the time of filing the instant application, I was involved in a double-blinded, placebo-controlled clinical trial to assess the effects of a formulation containing 6 g CLA and 500 mg NAC on 16 HIV-1 subjects with hyperlipidemia and lipodystrophy who were receiving anti-retroviral medication (the claimed patient population).

7.2.2. Over a twelve-week period, 16, male HIV-positive subjects with elevated serum lipids and exhibiting morphological changes were randomly assigned to the test powder formulation of conjugated linoleic acid (CLA) and N-acetylcysteine (NAC). The formulation delivered 6 g CLA and 500 mg NAC per day. For this study, a fruit-flavored powder containing the active ingredients was taken daily for 12 weeks. The placebo group received a non-active, isocaloric powder formulation consisting of safflower oil, maltodextrin and flavoring.

7.2.3. The study was a prospective, randomized, double-blinded, placebo-controlled clinical trial designed to evaluate the tolerability and provide limited safety and efficacy data of a dietary supplement containing 6 g CLA and 500 mg NAC (BION493 powder) on serum lipids and body fat distribution in HIV-infected patients taking HAART at a single center. Study design and protocol were approved by an independent review of the Copernicus Group Institutional Review Board (Cary, NC). Written informed consent was obtained from all study participants before enrollment.

7.2.4. Over a 12-week period, subjects (i) with a history of normal fat distribution, serum lipids and blood glucose prior to receiving ART and (ii) with fat redistribution, elevated serum lipids or glucose while receiving ART were randomly assigned to be given BION493 powder or an isocaloric placebo powder to be mixed with fluid and taken daily. Participants were seen in the clinic at baseline, at six weeks and at 12 weeks for evaluation.

7.2.5. At initiation, estimates of nutrient intake were made using a daily dietary recall form covering a period of three to seven days. All other evaluations were performed at baseline, six and twelve weeks. The serum lipid panel included total cholesterol, HDL cholesterol, LDL cholesterol (calculated) and triglycerides. Serum metabolic variables included fasting glucose, fasting insulin, alkaline phosphatase, urea nitrogen, sodium, total protein, potassium, creatinine, chloride, calcium, total bilirubin, carbon dioxide, alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

7.2.6. Anthropometric variables measured at baseline, six and twelve weeks included body weight (kg), height (cm), waist circumference (cm), hip circumference (cm), mid-biceps circumference (cm), wrist circumference (cm), mid-calf circumference (cm), ankle circumference (cm) and a bioelectrical impedance analysis (BIA). Computed

tomography (CT) scanning of abdomen and mid-thigh for assessing visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (ASAT) and extremity subcutaneous adipose tissue (ESAT) was performed at baseline and twelve weeks.

7.2.7. Complete blood counts were performed including total and differential leukocytes including platelets, HIV-1, RNA PCR 2$^{nd}$ generation with limit of detection < 50 copies and CD4 counts.

7.2.8. Assessment of compliance and request for adverse reactions was made at clinic visits two and three. Compliance was excellent in both the CLA/NAC formulation group as well as the placebo group. Comments on taste or mixability were reported by one subject in each treatment arm. For the purposes of this study, a serious adverse event was defined as any event that was fatal, life threatening, that is, the subject was, in the view of the investigator, at immediate risk of death as the event occurred, was disabling or incapacitating or required inpatient hospitalization. No serious adverse events occurred during this study.

7.2.9. Continuous variables were analyzed using analysis of variance procedures. The log transformation was used for all variables although the effect of compressing the distribution had little effect on the interpretation or power of the statistical analysis. The paired t-test was used to analyze differences within the groups from baseline to 6 weeks and from baseline to 12 weeks. The mean differences between groups at baseline, 6 weeks and 12 weeks were assessed with an unpaired t-test and with 95% confidence intervals calculated according to standard procedures. Medians were analyzed by the nonparametric Wilcoxin signed rank test. All tests were two-tailed and the probability of rejecting the Null hypothesis when true was set at the nominal 5% level. Statistical calculations were performed using Excell (Microsoft, Redmond, WA) and Data Desk software package (Data Desk, Ithaca, NY). The nonparametric Wilcoxin signed rank test for differences between medians provided the greatest power for detecting differences. Therefore all tables and figures were constructed using the median values with parenthetic minimum and maximum values to provide an estimate of variability.

7.2.10. Insulin sensitivity was calculated in the fasting state. The quantitative insulin sensitivity check index (QUICKI0 was used and calculated as the inverse of the sum of the logarithmic transformation of fasting concentrations of serum insulin and plasma glucose:

$$QUICKI(G_b,I_b) = (1/\log(G_b*I_b) = 1/(\log(G_b)+\log(I_b)$$

where Gb (mg/dL) is the fasting glucose concentration and Ib (μU/mL) is the fasting insulin concentration. This index has previously been shown to be a surrogate measure of insulin sensitivity, given the significant correlation with glucose disposal during euglycemic hyperinsulinemic glucose clamp tests.

7.2.11. Overall, 17 subjects were enrolled in the study, eight in the placebo and nine in the test group. One subject (CLA group) was eliminated for antiretroviral drug failure during the initial washout phase. Compliance was excellent in both the CLA formulation group as well as the placebo group. No serious adverse events occurred during this study. While individual estimates of exercise frequency, intensity, daily activity and energy were similar between the groups, differences in median age (placebo = 39, test = 47 years) and years since HIV-1 diagnosis (placebo = 10.5, test = 14.5) suggested an increase risk of dyslipidemia and lipoatrophy in the CLA formulation group. In the placebo group, four subjects were classified as category A, CDC AIDS status and two as category B status. The CLA formulation group had two category A, one category B and four category C (increasing severity and complications) subjects. Antiretroviral regimens for placebo and test subjects were comparable.

7.2.12. This double-blinded, placebo-controlled, safety and efficacy pilot study in 16 male, HIV-1 subjects receiving HAART demonstrated that a formulation containing CLA and NAC was safe and well tolerated over the 12 weeks.

7.2.13. As seen in **Figure 1**, daily consumption of the CLA formulation reduced LDL cholesterol from a median of 160 mg/dL at baseline to a median of 112 mg/dL by week 12 ($p<0.5$). Serum triglyceride concentrations rose two-fold in the placebo group over twelve weeks ($p<0.05$) but were not increased from baseline in the CLA formulation group ($p>0.05$). Additionally, the CLA formulation attenuated the two-fold increase observed in the triglyceride/HDL ratio in the placebo group by 26% at week 12 ($p<0.05$). No changes

were noted for total cholesterol, HDL cholesterol, cholesterol/HDL ratio or LDL/HDL ratio between treatments or over the 12 weeks of the study within treatments.

7.2.14. No differences were observed for fasting glucose or insulin concentrations between treatments or within treatments over the twelve weeks of the study. Further, no differences were seen in QUICKI values either between treatments or over time. However, the generally observed higher QUICKI values for the CLA formulation subjects indicating a more favorable insulin sensitivity was consistent with the lower insulin and triglyceride/HDL ratios seen in these subjects.

7.2.15. At week 12, both the placebo and CLA formulation groups had experienced increases in HIV-1 viral load. This increase was attenuated in the CLA formulation group compared to placebo subjects ($p<0.05$). CD4 cell counts were not affected by the CLA formulation and both the placebo and test groups exhibited no change over time.

7.2.16. While the placebo group lost 7.54 $cm^2$ of ESAT, the CLA group gained 0.82 $cm^2$ of ESAT. These values represent a 38% loss and 10 % gain of ESAT, respectively, for the placebo and CLA groups (**Figure 2**). This observation represents the first demonstration of the reversal of lipoatrophy by a food, supplement or drug.

7.2.17. The most dramatic and consistent effects of the CLA/NAC formulation were seen with serum lipid variables and ESAT values. Reduction of LDL cholesterol from 160 mg/dL at baseline was 20 percent within six weeks and 24 percent at twelve weeks. Additionally, the CLA/NAC formulation prevented the increase in triglycerides and attenuated the increase in triglyceride/HDL ratio seen in the placebo group.

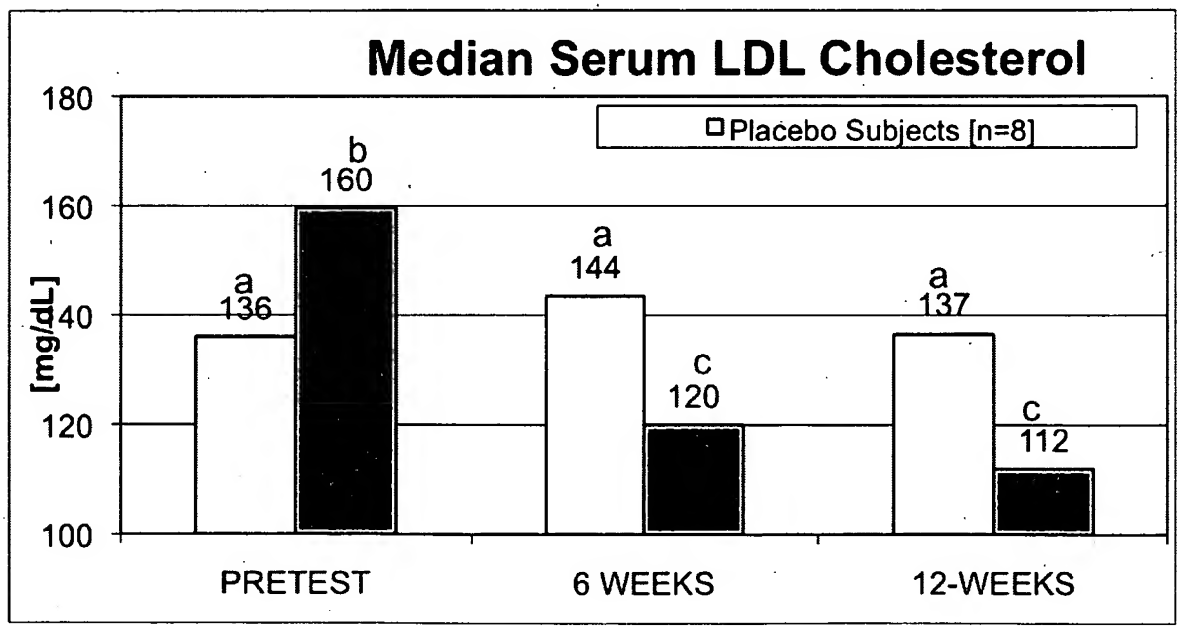
7.2.18. Attenuation of HIV-1 viral replication by the CLA formulation was also observed

7.2.19. Further, in this short-term study the CLA/NAC formulation did not decrease insulin sensitivity or adversely affect body composition. Since both insulin sensitivity and visceral adipose tissue are strongly associated with the triglyceride/HDL ratio, however, it is likely that the CLA/NAC formulation would demonstrate a positive effect on insulin sensitivity and body composition in an appropriately longer clinical trial.

7.2.20. In view of the inoperability of the prior art, these results were unexpected and represent a significant finding on the combination of CLA and NAC in the claimed patient population.

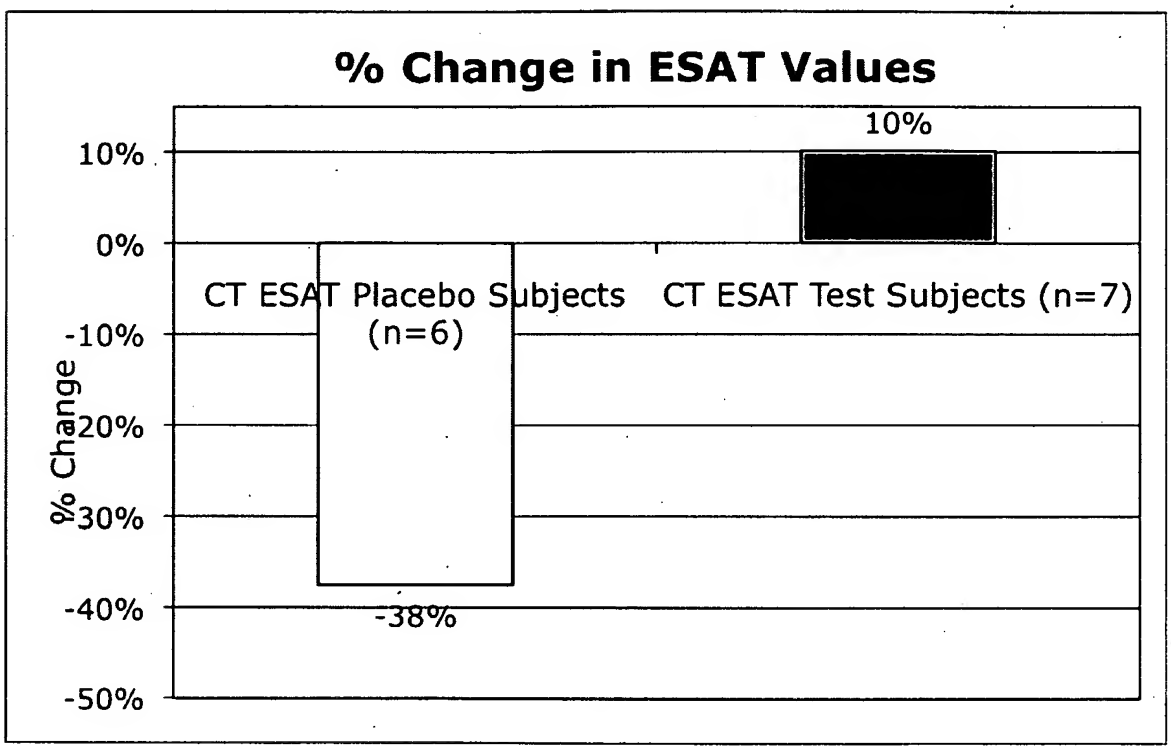
8. ***Conclusion.*** It is obvious from the above disclosure of the prior art concerning the inoperability of CLA or NAC for decreasing blood lipids or increasing subcutaneous fat clinically describes a situation in which neither Factor A nor Factor B functions successfully. The instant disclosure that the combination of two nonfunctioning factors results in a successful result is an example of the unexpected advantage of the claimed invention.

Figure 1. Serum LDL cholesterol in placebo and test subjects at pretest, six and twelve weeks.




**a,b,c-** Uncommon letters over treatment bars indicate differences between treatments are statistically different ($p<0.05$) as determined by the Wilcoxin signed rank test.

Figure 2. Percent change in median extremity subcutaneous adipose tissue (ESAT) in placebo and test subjects†




†ESAT differences between treatments are statistically different ($p<0.05$) as determined by the Wilcoxin signed rank test.

**Oath**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2/14/11

John G. Babish, Ph.D.
Chairman, Bionexus, Ltd.
Cornell Technology Park
30 Brown Road
Ithaca, NY 14850

# Curriculum Vitae Summary
## *John G. Babish, Ph.D.*

**Education:**

Bachelor of Science, Biochemistry – 1968
The Pennsylvania State University
State College, PA

Masters of Science, Chemistry - 1974
Cornell University, Ithaca, NY

Ph.D., Biochemistry - 1976
Cornell University, Ithaca, NY

**Employment History:**

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| **2004 – present:** | Consultant to the dietary supplement and pharmaceutical industries in the areas of inflammation, metabolic syndrome, diabetes, cancer and AIDS. BIOnexus laboratory performs contract research specializing in obesity, diabetes, inflammation and related cardiovascular diseases. Development of data for patent-protection of novel, nutritional products serving unmet health needs. |
| **1999 – 2004:** | Senior Vice President of Research & Development, MetaProteomics Research Laboratories, Ithaca, NY. Development of molecular techniques in proteomics related to the identification of pharmacological activity of natural products (60%). |
| **1998 – present:** | National Coordinator for the USDA Minor Species Drug Program (NRSP-7). The NRSP-7 program is funded by the USDA to provide funds and expertise necessary for the approval of pharmaceuticals used in the treatment of diseases associated with minor crop species. |
| **1997 – present:** | Co-founder and Chairperson of BIOnexus, Ltd., Ithaca, NY. |
| **1991 – 1996:** | Founder, Chairperson, President and CEO of Paracelsian, Inc., Ithaca, NY. |
| **1984 – 1996:** | Tenured, Associate Professor of Pharmacology and Toxicology, Department of Pharmacology, College of Veterinary Medicine, Cornell University, Ithaca, NY. |
| **1978 – 1984:** | Assistant Professor, Department of Preventive Medicine, NYS College of Veterinary Medicine, Cornell University, Ithaca, NY. |
| **1976 - 1978:** | Postdoctoral Scientist, Food and Drug Research Labs, Waverly, NY. |

**Invited Presentations (Representative of 40)**

*Minor Use, Minor Species Research – Species Grouping.* FDA/CVM Workshop Minor-Use and Minor Species: A Global Perspective. October 7th and 8th, 2004 Rockville, MD.

*Micronutrient deficiencies in AIDS wasting* at Progressive Management of AIDS Wasting: 2000. Hunter College, NYC. March 24, 2000.

*Phytochemicals and NF-kB activation* at IBC's Conference on The Health Benefits of Natural Phytoceuticals. Montreal Bonaventure Hilton, July 22 – 23, 1997.

*Chemically-induced cell cycle stasis in immunotoxicology.* 12th Annual NIOSH Conference on Mechanisms of Immunotoxicology – Role of Apoptosis in Immunotoxicology. University of West Virginia, Morgantown, WV. September 10 – 12, 1997.

**Abstracts Presented at Scientific Meetings (126)**

**Peer-reviewed Publications (106)**

1. Babish, J. G., Pacioretty, L. M., Bland, J. S., Minich, D. M., Hu, J., and Tripp, M. L. (2010) Antidiabetic Screening of Commercial Botanical Products in 3T3-L1 Adipocytes and *db/db* Mice, *J Med Food 13*, 535-547.
2. Lerman, R. H., Minich, D. M., Darland, G., Lamb, J. J., Schiltz, B., Babish, J. G., Bland, J. S., and Tripp, M. L. (2008) Enhancement of a modified Mediterranean-style, low glycemic load diet with specific phytochemicals improves cardiometabolic risk factors in subjects with metabolic syndrome and hypercholesterolemia in a randomized trial, *Nutr Metab (Lond) 5*, 29.
3. Hall, A. J., Babish, J. G., Darland, G. K., Carroll, B. J., Konda, V. R., Lerman, R. H., Bland, J. S., and Tripp, M. L. (2008) Safety, efficacy and anti-inflammatory activity of rho iso-alpha-acids from hops, *Phytochemistry 69*, 1534-1547.
4. Topic Popovic, N., Babish, J. G., and Bowser, P. R. (2007) Observational study of hepatic cytochrome P-450 protein expression and activity in summer flounder (Paralichtys dentatus) after combination ormetoprim-sulfadimethoxine treatment, *Chemotherapy 53*, 313-315.
5. Hall, A. J., Tripp, M., Howell, T., Darland, G., Bland, J. S., and Babish, J. G. (2006) Gastric mucosal cell model for estimating relative gastrointestinal toxicity of non-steroidal anti-inflammatory drugs, *Prostaglandins Leukot Essent Fatty Acids 75*, 9-17.
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10. Stoffregen, D. A., Wooster, G. A., Bustos, P. S., Bowser, P. R., and Babish, J. G. (1997) Multiple route and dose pharmacokinetics of enrofloxacin in juvenile Atlantic salmon, *J Vet Pharmacol Ther 20*, 111-123.
11. Rininger, J. A., Stoffregen, D. A., and Babish, J. G. (1997) Murine hepatic p53, RB, and CDK inhibitory protein expression following acute 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure, *Chemosphere 34*, 1557-1568.
12. Rininger, J. A., Ma, X., Stoffregen, D. A., Wheelock, G. D., and Babish, J. G. (1997) Chemical carcinogenesis as a consequence of cell cycle dysregulation, In *Proceedings of First World Molecular Toxicology Symposium*, Sophia-Antipolis, France.
13. Rininger, J. A., Goldsworthy, T. L., and Babish, J. G. (1997) Time course comparison of cell-cycle protein expression following partial hepatectomy and WY14,643-induced hepatic cell proliferation in F344 rats, *Carcinogenesis 18*, 935-941.
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15. Ma, X., Rininger, J. A., Chigurupati, P., Dong, H., and Babish, J. G. (1997) Biochemical pathways of inhibiting human immunodeficiency virus-1 replication and cytopathicity by andrographolide, *Abstr Gen Meet Am Soc Microbiol 97*, 538.
16. Wheelock, G. D., Hurst, K. R., and Babish, J. G. (1996) Bioimmunoassay of Aryl Hydrocarbon (Ah) Receptor Transformation in Vitro by 2,3,7,8- Tetrachlorodibenzo-p-Dioxin(TCDD), *Toxicology Mechanisms and Methods 6*, 41-50.
17. Vancutsem, P. M., and Babish, J. G. (1996) In vitro and in vivo study of the effects of enrofloxacin on hepatic cytochrome P-450. Potential for drug interactions, *Vet Hum Toxicol 38*, 254-259.
18. Sweeney, L. M., Shuler, M. L., Quick, D. J., and Babish, J. G. (1996) A preliminary physiologically based pharmacokinetic model for naphthalene and naphthalene oxide in mice and rats, *Ann Biomed Eng 24*, 305-320.
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**Book Chapters**

Babish, J. G., and Ma, X. (2002) Biological and pharmacological therapeutics: Andrographolide, In *AIDS and Complementary and alternative Medicine* (Standish, L. J., Calabrese, C., and Galantino, M. L., Eds.) 1 ed., Elsevier Health Sciences, St. Louis, MO.

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**Patents (32 US and five foreign patents/Patent Applications (40 US and 39 foreign)**

1. US Patent No. **7,820,206** (10/26/10) Modulation of inflammation by hops fractions and derivatives.
2. US Patent No. **7,815,944** (10/19/2010) Anti-inflammatory pharmaceutical compositions for reducing inflammation and the treatment and prevention of gastric toxicity

3. US Patent No. **7,811,610** (10/12/2010) Anti-inflammatory pharmaceutical compositions for reducing inflammation and the treatment and prevention of gastric toxicity
4. US Patent No. **7,807,203** (10/5/2010) Anti-inflammatory pharmaceutical compositions for reducing inflammation and the treatment and prevention of gastric toxicity
5. US Patent No. **7,794,757** (9/14/2010) Modulation of inflammation by hops fractions and derivatives
6. US Patent No. **7,790,205** (9/7/2010) Synergistic compositions that treat or inhibit pathological conditions associated with inflammatory response.
7. US Patent No. **7,736,677** (6/15/2010) Xanthohumol and tetrahydro-isoalpha acid based protein kinase modulation cancer treatment
8. US Patent No. **7,722,903** (5/25/2010) Modulation of inflammation by hops fractions and derivatives
9. US Patent NO. 7, **682,636** (3/23/2010) Curcuminoid compositions exhibiting synergistic inhibition of the expression and/or activity of cyclooxygenase-2
10. US Patent No. **7,666,449** (2/23/2010) Anti-inflammatory pharmaceutical compositions for reducing inflammation and the treatment or prevention of gastric toxicity
11. US Patent No. **7,431,948** (10/7/2008) Compositions that treat or inhibit pathological conditions associated with inflammatory response
12. US Patent No. **7,332,185** (2/19/2008) Complex mixtures exhibiting selective inhibition of cyclooxygenase-2
13. US Patent No. **7,279,185** (10/9/2007) Curcuminoid compositions exhibiting synergistic inhibition of the expression and/or activity of cyclooxygenase-2
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15. US Patent No. **7,205,151** (4/17/2007) Complex mixtures exhibiting selective inhibition of cyclooxygenase-2
16. US Patent No. **7,195,785** (3/27/2007) Complex mixtures exhibiting selective inhibition of cyclooxygenase-2
17. US Patent No. **6,979,470** (12/27/2005) Curcuminoid compositions exhibiting synergistic inhibition of the expression and/or activity of cyclooxygenase-2
18. US Patent No. **6,908,630** (6/2120/05) Combinations of sesquiterpene lactones and ditepene triepoxide lactones for synergistic inhibition of cyclooxygenase-2
19. US Patent No. **6,780,596** (8/24/2004) Methods for determining the activity of complex mixtures
20. US Patent No. **6,733,793** (5/11/2004) Oral composition with insulin-like activities and methods of use
21. US Patent No. **6,629,835** (11/7/2003) Combinations of diterpene triepoxide lactones and ditepene lactones or triterpenes for synergistic inhibition of cyclooxygenase-2

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23. US Patent No. **6,140,063** (10/31/2000) In vitro screening assay for identification of compounds that inhibit cytopathicity of viral infection
24. US Patent No. **5,833,994** (11/10/1998) Use of the Ah receptor and Ah receptor ligands to treat or prevent cytopathicity of viral infection.
25. US Patent No. **5,612,188** (3/18/1997) Automated, multicompartmental cell culture system.
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